fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

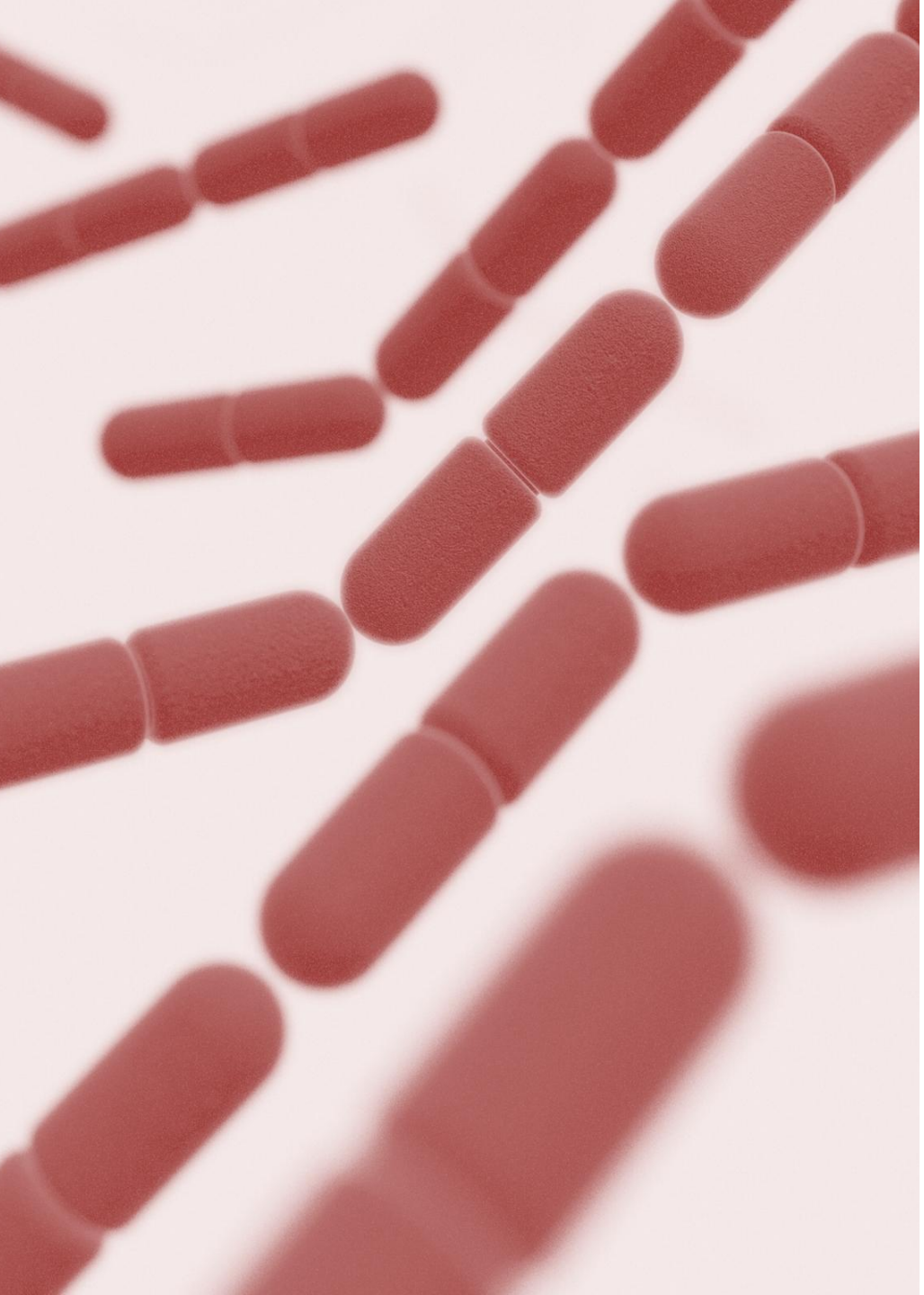
Consensus GIMEMA

sulla profilassi antimicrobica nei pazienti adulti affetti da leucemia mieloide acuta (LMA).

a cura del Working Party Infezioni
e del Working Party Leucemie Acute

Fondazione GIMEMA

con il contributo di AIL



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Questo documento rappresenta una versione preliminare e non definitiva del Consensus elaborato dal GIMEMA WP Leucemie acute e Infezioni. Non costituisce una linea guida ufficiale né una pubblicazione scientifica sottoposta a peer review. I contenuti riflettono lo stato delle conoscenze e delle opinioni condivise al momento della redazione e potranno essere oggetto di successive revisioni, aggiornamenti o integrazioni, anche in vista di una pubblicazione scientifica formale.
Il documento non è rivolto direttamente ai pazienti: è destinato all'utilizzo da parte di professionisti sanitari, che sono tenuti a valutarne criticamente le indicazioni e ad applicarle nel rispetto del proprio giudizio clinico e delle normative vigenti.

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Induction intensive chemotherapy in AML non APL

PROPHYLAXIS	LITERATURE EVIDENCE AND EP (EXPERT PANEL OPINION)	RECOMMENDATIONS, PROPHYLAXIS GOALS AND CONSIDERATIONS
Antibacterial prophylaxis (ABP)	Literature data in AML patients show that bacterial infections, particularly gram-negative infections, represent a life-threatening complication and ABP: • does not impact on survival • reduces febrile episodes • reduces Gram negative infections • There is no clear evidence that ABP is responsible for the increase of MDR infections in AML in-patient population.	ABP with FQ (fluoroquinolones) may be considered during neutropenia after induction intensive chemotherapy. Monitoring of patient colonization by MDR bacteria and of local epidemiology is recommended. **The goal of ABP is to prevent a severe complication that may interfere with the leukemia treatment schedule.**
Antifungal prophylaxis (AFP)	Literature data show that invasive fungal infections represent a life-threatening complications and AFP: • is associated with improved survival • reduces invasive fungal infections • is not associated with an increase of resistant fungal pathogens.	AFP with posaconazole (preferably tablet formulation) is recommended until complete remission and/or neutrophilis recovery. In patients treated with intensive chemotherapy + FLT3 inhibitors AFP is recommended but caution and careful monitoring for cardiac toxicity should be used, particularly in older patients. **The goal of AFP is to prevent a life-threatening infection that may interfere with the leukemia treatment schedule.**
HSV/VZV antiviral prophylaxis (AVP)	Literature data show that HSV and VZV infections rarely are severe complications and AVP: • does not impact on survival • prevents HSV and VZV infections Some EP members hypothesize that AVP may be able to mitigate chemotherapy induced oral mucositis.	HSV-seropositive and VZV-seropositive patients should receive AVP (acyclovir, valacyclovir or famciclovir) for 3–5 weeks after the start of chemotherapy. In patients receiving HZ vaccination AVP is administered with the aim to prevent HSV infections. **The goal of AFP is to prevent an infection that may impact on patient's quality of life.**
Anti-PJP prophylaxis	Literature data do not report an increased risk of PJP in AML patients and there is no experience on the use of anti-PJP prophylaxis. According to the EP, there is an increase of PJP risk in pazients receiving fludarabine-based induction chemotherapy.	Anti-PJP prophylaxis is not recommended with the exception of patients receiving fludarabine-based chemotherapy regimens. In those patients, anti-PJP prophylaxis is suggested and should be continued until the CD4 count remains <200/mcL.

Induction (chemo-based or ATO-based) in APL

PROPHYLAXIS	LITERATURE EVIDENCE AND EP (EXPERT PANEL OPINION)	RECOMMENDATIONS, PROPHYLAXIS GOALS AND CONSIDERATIONS
Antibacterial prophylaxis (ABP)	Recent literature does not offer specific information on the ABP in APL patients. However, the EP agrees that data available in AML patients can be translated into the APL setting. Literature data in AML patients show that ABP: • does not impact on survival • reduces febrile episodes • reduces Gram negative infections • There is no clear evidence that ABP is responsible for the increase of MDR infections in APL in-patient population.	ABP with FQ may be considered during neutropenia after chemo-based induction intensive chemotherapy and in patients receiving ATO-based induction regimens in case of prolonged and severe neutropenia or concomitant risk factors (i.e. smoking, advanced age, COPD). Monitoring of patient colonization by MDR bacteria and of local epidemiology is recommended. **The goal of ABP is to prevent a severe complication that may interfere with the leukemia treatment schedule.**
Antifungal prophylaxis (AFP)	Literature data show a low risk of invasive fungal infections in APL patients.	AFP is not generally recommended, due to the low risk of invasive fungal disease in this setting, regardless of treatment schedule. In centers with high rate of mould infections, AFP may be considered in chemo-based induction regimens with **the goal to prevent a life-threatening infection that may interfere with the leukemia treatment schedule.**
HSV/VZV antiviral prophylaxis (AVP)	Literature data show that patients receiving ATO-based regimens are at high risk of HZ infections until several months after ATO discontinuation.	All patients receiving ATO-based regimens should receive AVP (acyclovir, valacyclovir), until 6 months after ATO discontinuation **The goal of AVP to prevent HZ infection in APL receiving ATO is to prevent an infection and related complication that may impact on patient's quality of life.**
Anti-PJP prophylaxis	Literature data do not report an increased risk of PJP in APL patients and there is no experience on the use of anti-PJP prophylaxis.	Anti-PJP prophylaxis is not recommended.

Less intensive regimens (HMA + Venetoclax)

PROPHYLAXIS	LITERATURE EVIDENCE AND EP (EXPERT PANEL OPINION)	RECOMMENDATIONS, PROPHYLAXIS GOALS AND CONSIDERATIONS
Antibacterial prophylaxis (ABP)	Literature data show an high risk of bacterial infections particularly during the first 2 cycles of treatment. High infectious risk may be prolonged in patients with late or no response to treatment and with prolonged neutropenia. There are not recent specific data on the ABP in this setting. However, the EP agrees that information from AML patients receiving intensive chemotherapy can be translated into the less intensive regimens setting. Literature data in AML patients show that ABP: • does not impact on survival • reduces febrile episodes • reduces Gram negative infections • There is no clear evidence that ABP is responsible for the increase of MDR infections in the AML out-patient population.	ABP with FQ may be considered in the first cycles (starting at the end of the rump-up) or until neutrophilis recovery; then, in the post-remission phase, ABP may be considered only if grade 4 neutropenia occurs. Monitoring of patient colonization by MDR bacteria and of local epidemiology is recommended. **The goal of ABP in out-patients treated with HMA and venetoclax is to prevent any complication (including fever of unknown origin) representing a potential risk for hospitalization.**
Antifungal prophylaxis (AFP)	Literature data show a high risk of invasive fungal infections particularly during the first cycles of treatment.	AFP with posaconazole (preferably tablet formulation) is recommended in the first cycles, starting at the end of the rump-up. It shoud be taken in mind the well known venetoclax dose reduction when posaconazole is concomitantly administered. When a CR is achieved, AFP should be given only in case of grade 4 prolonged neutropenia. **The goal of AFP is to prevent life-threatening infections that may also interfere with the leukemia treatment schedule.**
HSV/VZV antiviral prophylaxis (AVP)	Literature data do not report frequent or severe HSV or VZV infections during HMA and venetoclax treatment.	AVP is not recommended.
Anti-PJP prophylaxis	Literature data do not report an increased risk of PJP in patients treated with HMA and venetoclax.	Anti-PJP prophylaxis is not recommended.

Less intensive regimens (HMA alone or HMA + Ivosidenib or LDAC + Glasdegib)

PROPHYLAXIS	LITERATURE EVIDENCE AND EP (EXPERT PANEL OPINION)	RECOMMENDATIONS, PROPHYLAXIS GOALS AND CONSIDERATIONS
Antibacterial prophylaxis (ABP)	Literature data show a moderate risk of bacterial infections particularly during the first 2 cycles of treatment. High infectious risk may be prolonged in patients with late or no response to treatment and with prolonged neutropenia. There are not recent specific data on the ABP in this setting. However, the EP agrees that information from AML patients receiving intensive chemotherapy can be translated into the less intensive regimens setting. Literature data in AML patients show that ABP: • does not impact on survival • reduces febrile episodes • reduces Gram negative infections • There is no clear evidence that ABP is responsible for the increase of MDR infections in the AML out-patient population.	ABP with FQ may be considered in the first cycles, or until neutrophilis recovery; then, in the post-remission phase, ABP may be considered only if grade 4 neutropenia occurred. Monitoring of patient colonization by MDR bacteria and of local epidemiology is recommended. **The goal of ABP in out-patients treated with HMA alone or combined with ivosidenib and with LDAC + Glasdegib is to prevent any complication (including fever of unknown origin) representing a potential risk for hospitalization.**
Antifungal prophylaxis (AFP)	Literature data show a moderate risk of invasive fungal infections particularly during the first cycles of treatment.	AFP with posaconazole (preferably tablet formulation) may be considered in the first cycles. When a CR is achieved, AFP should be given only in case of grade 4 prolonged neutropenia. In patients who receive ivosidenib in association with HMA or glasdegib in association with LDAC, DDI and possible QTc prolongation should be taken into account. **The goal of AFP is to prevent life-threatening infections that may also interfere with the leukemia treatment schedule.**
HSV/VZV antiviral prophylaxis (AVP)	Literature data do not report frequent or severe HSV or VZV infections during HMA alone or combined with ivosidenib or LDAC + Glasdegib.	AVP is not recommended.
Anti-PJP prophylaxis	Literature data do not report an increased risk of PJP in patients treated with HMA alone or combined with ivosidenib or LDAC + Glasdegib	Anti-PJP prophylaxis is not recommended.

Best supportive care/palliative care

PROPHYLAXIS	LITERATURE EVIDENCE AND EP (EXPERT PANEL OPINION)	RECOMMENDATIONS, PROPHYLAXIS GOALS AND CONSIDERATIONS
Antibacterial prophylaxis (ABP)	There are not extensive literature on bacterial infections in patients ineligibile for any treatment undergoing best supportive care/palliative care.	ABP with FQ is not recommended. It is reasonable to consider ABP with FQ on a patient-by-patient basis, **with the intent to preserve quality of life and minimize healthcare resource utilization**.
Antifungal prophylaxis (AFP)	There are not extensive literature on fungal infections in patients ineligibile for any treatment undergoing best supportive care/palliative care.	AFP in this setting is not recommended.
HSV/VZV antiviral prophylaxis (AVP)	There are not extensive literature on viral infections in patients ineligibile for any treatment undergoing best supportive care/palliative care.	AVP is not recommended.
Anti-PJP prophylaxis	There are not extensive literature on PJP infections in patients ineligibile for any treatment undergoing best supportive care/palliative care.	Anti-PJP prophylaxis is not recommended.

Vaccinations in AML

VACCINE	LITERATURE EVIDENCE AND EP (EXPERT PANEL OPINION)	RECOMMENDATIONS, PROPHYLAXIS GOALS AND CONSIDERATIONS
Pneumococcal	Literature data show a more than 20 times higher risk of invasive pneumococcal disease in AML patients compared to the general population, particularly in the elderly setting. Various studies show a good response to vaccination in patients with myeloprolipherative diseases, including AML out of the chemotherapy period.	Pneumococcal vaccination with 20-valent pneumococcal conjugate vaccine (PCV-20) (single dose) is recommended in all AML patients particularly in older patients (≥ 65 years). It should be administered preferentially before starting antileukemic therapy. If delivery of vaccination is not feasible before therapy start, it can be administered at any time in less intensive treatments and after treatment discontinuation in patients submitted to intensive chemotherapy. **The goal of pneumococcal vaccination is to prevent a life-threatening infection, one of the most frequent causes of community acquired pneumonia, which could also interfere with the leukemia treatment schedule.**
HZ	Literature data show a moderately higher risk of HZ infection in AML patients compared to the general population. Various studies show a good response to HZ vaccination in patients with myeloprolipherative diseases.	HZ vaccination with adjuvated recombinant zoster vaccine (two doses at least one month apart) should be administered preferentially before starting antileukemic therapy, particularly in older patients (≥ 65 years). If delivery of vaccination is not feasible before therapy start, it can be administered at any time in less intensive treatments. In patients submitted to intensive chemotherapy particularly if receiving AVP during chemotherapy HZ vaccination can be postponed after chemotherapy discontinuation. **The goal of HZ vaccination is to prevent a complication that may interfere with the leukemia treatment schedule and may impact on the patients's quality of life, particularly if complicated by post-herpetic neuropaty**
Influenza	Literature does not report recent specific epidemiological and clinical data of influenza virus infection in AML patients but the EP agrees that influenza may be serious complication in AML, particularly in elderly patients. Various studies show a good response to influenza vaccination in patients with myeloprolipherative diseases.	Seasonal (once a year) influenza vaccination with adjuvated flu vaccine is recommended particularly in elderly patients. **The goal of influenza vaccination is to prevent a severe complication that may interfere with the leukemia treatment schedule.**
SARS CoV 2	Literature data show a poorer outcome of SARS-CoV-2 infections in patients with hematological malignancies, including AML patients, compared to the general population, also in the Omicron era. A good response to vaccination has been reported in patients with myeloprolipherative diseses, including AML patients.	SARS-CoV-2 vaccination (at least once a year) is recommended particularly in elderly patients. **The goal of SARS CoV-2 vaccination is to prevent a life-threatening complication that may interfere with the leukemia treatment schedule.**

HBV prophylaxis

RECOMMENDATIONS, PROPHYLAXIS GOALS AND CONSIDERATIONS

All HBsAg-positive patients, regardless HBV DNA levels, should receive anti-HBV drugs. The use of third-generation antiviral drugs (entecavir, tenofovir or tenofovir alafenamide) is recommended in HBsAg-positive AML patients regardless of HBV DNA levels. Antiviral prophylaxis should be initiated at least 1 week before or in concomitance with starting chemotherapy. It should be continued for the duration of chemotherapy and should be administered for at least 12 to 24 months after chemotherapy withdrawal. Subsequent monitoring for delayed HBV reactivation after the cessation of antiviral prophylaxis is essential.

HBsAg-negative, anti-HBc-positive patients should receive antiviral prophylaxis or follow patients without prophylaxis by serology and quantitative HBV DNA. The recommended prophylaxis drug is lamivudine. Lamivudine should be initiated at least 1 week before or in concomitance with starting chemotherapy. It should be continued for the duration of chemotherapy and should be administered for at least 18 months after chemotherapy withdrawal. Quantitative HBV DNA monitoring is also recommended during lamivudine prophylaxis.

The goal of HBV prophylaxis is to prevent HBV reactivation and liver disease that could be a life-threatening complication that may also interfere with the leukemia treatment schedule.


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